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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/803,578	03/09/2001	Patrick Hwu	2026-4341	6841

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EXAMINER	
WILSON, MICHAEL C	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 05/27/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/803,578	HWU ET AL.	
	Examiner	Art Unit	
	Michael C. Wilson	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 March 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4,7,8,10,11,40,41,44-61 and 71-82* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,7,8,10,11,40,41,44-61 and 71-82* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3-23-05 has been entered.

Claims 2, 3, 5, 6, 9, 12-39, 42, 43 and 62-70 have been cancelled. Claims 72-82 have been added. Claims 1, 4, 7, 8, 10, 11, 40, 41, 44-61 and 71-82 are pending and under consideration in the instant office action.

Applicant's arguments filed 6-29-04 have been fully considered but they are not persuasive.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Election/Restrictions

Claims 1, 4, 7, 8, 10, 11, 40, 41, 44-61 and 71-82 are under consideration in the instant office action.

Claim 1 is under consideration in the instant office action as it relates to a T lymphocyte having i) a recombinant MOv-γ receptor or a recombinant T-cell receptor

(TCR) that reacts with an ovarian tumor antigen, and ii) an "endogenous" TCR that reacts with a cell that is allogeneic to the lymphocyte.

Claim 11 is under consideration as it relates to a lymphocyte having i) a TCR that reacts with a cell that is allogeneic to the lymphocyte, and ii) an MOv-γ receptor that reacts with an ovarian tumor antigen.

Claim 40 is under consideration as it relates to a pharmaceutical composition comprising lymphocytes having i) a recombinant MOv-γ receptor reactive with an ovarian tumor antigen, and ii) an "endogenous" TCR that reacts with a cell that is allogeneic to the lymphocyte.

Claim 41 is under consideration as it relates to a method of preparing lymphocytes having dual specificity by i) contacting lymphocytes with a cell that is allogeneic to the lymphocyte, and ii) transducing the lymphocyte with an MOv-γ that reacts with an ovarian tumor antigen.

Claims 72 is under consideration in the instant office action as it relates to a T lymphocyte having i) a recombinant T-cell receptor (TCR) that is reactive with an ovarian tumor antigen, and ii) an "endogenous" TCR reactive with a cell that is allogeneic to the lymphocyte.

Claims 77 and 78 are under consideration in the instant office action as it relates to a T lymphocyte having i) a recombinant chimeric T-cell receptor (TCR) that reacts with an ovarian tumor antigen, and ii) an "endogenous" TCR that reacts with a cell that is allogeneic to the lymphocyte.

Claim 79 is under consideration in the instant office action as it relates to a T lymphocyte having i) a recombinant chimeric T-cell receptor (TCR) that reacts with an ovarian tumor antigen, and ii) a TCR that reacts with a cell that is allogeneic to the lymphocyte.

Claim 81 is under consideration in the instant office action as it relates to a T lymphocyte having i) a recombinant T-cell receptor (TCR) that reacts with an ovarian tumor antigen, and ii) a TCR that reacts with a cell that is allogeneic to the lymphocyte.

Specification

The status of application 08/547263, cited on pg 17, line 5, will need to be updated as necessary.

Claim Objections

The phrase "a cell, which cell is" in claims 1, 11, 40 has been changed to --a cell that is--.

Claim Rejections - 35 USC ' 112

New Matter

The rejection regarding the scope of lymphocytes having a second receptor that recognizes any cell that is allogeneic to the lymphocyte has been withdrawn partly in view of applicants' arguments.

Applicants point to pg 11, ¶ 42, which states:

> "'Dual specificity lymphocytes' as that phrase is used herein refers to lymphocytes capable of reacting with both a tumor antigen and a pre-selected strong antigen. The tumor antigen reactivity may be conferred by genetically modifying lymphocytes with a chimeric T cell receptor gene encoding a binding site for the tumor antigen. Tumor antigen reactivity may also be conferred by native TCR itself. Reactivity with the pre-selected strong antigens) is preferably conferred by in vitro expansion of the isolated population of lymphocytes by specific T cell activation using one or more pre-selected strong antigens."

Applicants point to pg 17, ¶ 53, lines 3-7, which states:

> "In one embodiment, the specific expansion step amplifies an individual or a subpopulation of T cells whose endogenous TCR is directed to the strong antigen(s) used to expand the T cells."

Applicants point to original claims 1, 2 and 11:

> 1. A composition comprising a preselected population of lymphocytes having a chimeric receptor or T-cell receptor reactive with a tumor antigen and an endogenous receptor reactive with a preselected strong antigen. (emphasis added).
> 2. The composition of claim 1, wherein the strong antigen is an allogeneic agent.
> 11. A lymphocyte having a T-cell receptor reactive with an allogeneic agent and a chimeric receptor reactive with a tumor antigen.

Claim 1, 2 and 11 in view of pg 11, ¶ 41, supports the breadth of a T-lymphocyte having

a TCR reactive with any cell that is allogeneic to the T-cell as claimed

Pg 11, ¶ 41 states:

> "The lymphocytes of the present invention are pre-selected for TCRs having reactivity with specific antigens. These antigens are preferably strong antigens. The term 'strong antigen' as it is referred to herein relates to an antigen capable of inducing proliferation of pre-selected adoptively transferred T cells. Examples of such antigens include but are not limited to alloantigens, viral agents and other foreign agents. Allogeneic agents or 'alloantigens' are antigens derived from genetically non-identical members of the same species. Allogeneic tissues, cells, proteins, peptides, nucleic acids and/or other cellular components may be used to select an individual or subpopulation of lymphocytes."

It is readily apparent that the allogeneic agent in claims 2 or 11 can be the allogeneic cells in ¶ 41 "used to select an individual or subpopulation of lymphocytes" in context of ¶ 41.

It is noted that applicants' arguments regarding Examples 3-9 and 11 were not found persuasive because the examples do not support the breadth of a T-lymphocyte having a TCR reactive with any cell that is allogeneic to the T-cell as claimed.

Applicants' arguments regarding support for T-cells having an endogenous TCR reactive with PBMCs, dendritic cells or B-cells that are allogeneic to the T-cells are persuasive. Pg 35, ¶ 83, describes stimulating PBMC with allogeneic PBMC, B-cells or dendritic cells, which can only occur if the T-cells have a TCR that recognizes the PBMC, B-cells or dendritic cells. See also Fig. 12A-D as discussed in ¶ 4 of the Declaration by Dr. Hwu.

I. Claims 46, 50, 56 and 58 remain rejected and new claims 75 and 79-82 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for reasons of record.

T lymphocyte having two receptors comprising 1) an MOv-γ receptor, and 2) an endogenous receptor that reacts with a splenocyte that is allogeneic to the lymphocyte (claims 46, 50, 56 and 58) remains new matter.

Applicants argue:

> "Although the specification does not explicitly demonstrate reaction with allogeneic splenocytes, the reaction is implicit to the teachings of the instant specification, such that one of ordinary skill in the art would conclude that the T-cells described in Example 5 had such an endogenous T-cells receptor. Because the specification states that the T-cells were "dual specificity allogeneic MOv-y T-cells" and that mice injected with these cells were immunized with allogeneic splenocytes (page 30, paragraph 79 of Example 5), one of ordinary skill in the art would conclude that the dual specificity T-cells had an endogenous receptor reactive with an allogeneic splenocyte.
>
> Furthermore, Figure 5 demonstrates that the tumor-bearing mice injected with both allogeneic splenocytes and dual specificity T-cells became tumor-free. As stated in paragraph 3 of the Declaration of Dr. Patrick Hwu, the fact that the tumor-bearing mice became tumor-gee under these conditions shows that the allogeneic splenocytes reacted w1t11 the endogenous T-cell receptors of the dual specificity T-cells, thereby causing the dual specificity T-cells to clonally expand in the mice, which, in turn, allowed the mice to become tumor-free. Therefore, given the explicit and implicit teachings of Example 5, T lymphocytes comprising an MOv-y receptor and an endogenous receptor reactive with an allogeneic splenocyte is not new matter." (pg 10 of response).

Applicants' arguments regarding support for T-cells having an endogenous TCR reactive with a splenocytes are not persuasive. Pg 30, ¶ 79 teaches "dual specificity allogeneic/MOv-γ T cells" but does not teach the "dual specificity" was to splenocytes. The Example describes mice immunized with splenocytes and the dual specific T-cells, but does not describe the T-cells were "reactive with" the splenocytes. Therefore, one of ordinary skill in the art could not conclude that the dual specificity T-cells had an endogenous receptor reactive with an allogeneic splenocytes as asserted by applicants. The declaration by Dr. Hwu has been considered but is not persuasive regarding the

asserted implications in the specification as originally filed. Dr. Hwu states: "The fact that the tumor-bearing mice became tumor-free under these conditions show that the allogeneic splenocytes reacted with the endogenous T-cell receptors of the dual specificity T-cells, thereby causing the dual specificity T-cells to clonally expand in the mice, which, in turn, allowed the mice to become tumor-free." The declaration is not persuasive because the tumor-bearing mice may have become tumor-free simply because the T-cells had a TCR specific for the tumor. The specification does not describe the T-cells as being stimulated by the splenocytes.

The limitation of T-cells "exposed to a cell that is allogeneic to at least one of the T-lymphocytes of the population under conditions which expand and activate the T lymphocytes" in claims 79 and 81 is new matter. The breadth of exposing T-cells to **a** cell that is allogeneic to at least one of the T lymphocytes does not have support on pg 31-32. The phrase "under conditions which expand and activate the T lymphocytes" does not have support on pg 31-32.

The limitation of a population of T lymphocytes that "substantially consists of" T-cells reactive with the allogeneic cells in claims 80 and 82 does not have support in the specification as originally filed. In particular, the breadth of "substantially consists of" is not described in the specification. Applicants point to pg 17, ¶ 35, which states:

> "Specific expansion and specific activation of the T cells containing the chimeric T-cell receptor gene are important parts of the present invention. In one embodiment, the specific expansion step amplifies an individual or a subpopulation of T cells whose endogenous TCR is directed to the strong antigen(s) used to expand the T cells. In this way, T cells which react with the antigen(s) are selected out and amplified from a mixed population of T cells originally obtained from the patient. The expanded lymphocytes are transduced with a chimeric receptor gene. These pre-selected, transduced T cells are

> introduced into a patient, and the patient is immunized with the strong antigens). This in vivo immunization step serves to activate the pre-selected adoptively transferred T cells and to target the lymphocytes to the cancer antigen through the chimeric receptor."

However, ¶ 35 does not contemplate the breadth of the phrase "substantially consists of" as newly amended.

Written Description

The rejection regarding claims 1, 3, 4, 7, 8, 10, 11, 40, 41, 44-61 and 71 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention has been withdrawn.

The "chimeric receptor reactive with a tumor antigen" (1, 11, 40, 41, 77 and 79) and "recombinant T-cell receptor, which is reactive with a tumor antigen" (claim 72, 78 and 81) has written description given the teachings in the specification taken with the art at the time of filing. Applicants argue many chimeric receptors reactive with a tumor antigen as claimed were known in the art. Applicants' arguments are persuasive. For example, Darcy cited by applicants taught such a receptor on pg 3706, col. 1, 2nd ¶, Haynes taught such a receptor on pg 183, col. 1, 3rd ¶ and Weijtens (1996) cited by applicants taught such a receptor in the abstract and on pg 837, col. 1, 1st full ¶. It is noted that Dakappagari cited by applicants taught a chimeric peptide but did not teach a chimeric receptor as claimed.

Indefiniteness

The rejection of claims 1, 4, 7, 8, 10, 11, 40, 41, 44-61 and 71 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention has been withdrawn. Use of a "recombinant T-cell receptor" that recognizes a tumor antigen has been deleted from claim 1 a).

Claim Rejections - 35 USC ' 102

II. Claims 1, 3, 4, 7, 8, 10, 11, 40, 44-61 and 71 remain rejected and claims 72-78 are rejected under 35 U.S.C. 102(e) as being anticipated by Nishimura (US Patent 5,830,755) as supported by Shileyansky (PNAS, March 1994, Vol. 91, pg 2829-2833), Nishimura (J. Immunotherapy, 1994, Vol. 16, pg 85-94), Wang (J. Immunol., 1995, Vol. 154, pg 1797-1903) and Cole (Cancer Res., Dec. 1, 1997, Vol. 57, pg 5320-5327), all of record.

Nishimura taught isolating tumor infiltrating lymphocytes (TIL) from colon adenocarcinoma, stimulating the TIL with antigen and transfecting the cells with a chimeric receptor, MOv-γ, that reacts with ovarian tumors ("38 Tumor") (Example 4, col. 35-39; see ¶ bridging col. 37-38; col. 38, lines 11-13; col. 39, Table 8, "38 MOv-TIL" and "38 Tumor"). The TIL inherently have an "endogenous T-cell receptor reactive with a cell that is allogeneic to the lymphocyte" because transduced and non-transduced TIL

reacted with murine sarcoma cells (24 JK) in an IFN-γ ELISA (col. 39, Table 8; TIL NV and 24 JK).

Interpretation 1 has been withdrawn. In interpretation 1, the examiner asserted the transduced TIL had two receptors: the MOv-γ chimeric receptor, and a receptor that recognizes the cell line 24 JK (as evidenced by the results in col. 39, Table 8 (TIL NV and 24 JK)). The examiner asserted the 24 JK cell line was "allogeneic" to the TIL of Nishimura. "Allogeneic" is defined as "having cell types that are antigenically distinct" (see definition from Dorland's Medical Dictionary provided). The examiner asserted the JK24 cells were "antigenically distinct" to the transduced TIL because they had low expression of MHC Class I molecules as compared to clone 4JK (see abstract from Shiloni, 1993, Cancer Immunology, immunotherapy, Vol. 37, pg 286-292; lines 3-9).

Applicants argue the term "allogeneic" can also be defined as "individuals (or tissues) that are of the same species but antigenically distinct, as opposed to syngeneic and xenogeneic." Applicants point to ¶ 41 of the specification on pg 11, which states: "Allogeneic agents or 'alloantigens' are antigens derived from genetically non-identical members of the same species." Therefore, applicants conclude that the definition of allogeneic in light of the specification must be limited agents from genetically non-identical members of the same species." Applicants' arguments are persuasive. Interpretation 1 is hereby withdrawn because the term "allogeneic" is limited to agents from genetically non-identical members of the same species and because the Declaration by Dr. Hwu states the 24JK cells are syngeneic to the TIL and not allogeneic to the TIL.

Interpretation 2: the transduced TIL have two receptors: the MOv-γ chimeric receptor, and an endogenous T-cell receptor that recognizes an allogeneic cell. The second receptor is inherent in the population of transduced TIL described by Nishimura because a population of TIL has a diverse array of endogenous TCRs. One of the many endogenous TCRs present in the population of transduced TIL must recognize at least one allogeneic cell. Therefore, the TIL of Nishimura inherently have an endogenous TCR that recognizes allogeneic cells. Evidence is provided by Shileyansky (PNAS, March 1994, Vol. 91, pg 2829-2833), Nishimura (J. Immunotherapy, 1994, Vol. 16, pg 85-94), Wang (J. Immunol., 1995, Vol. 154, pg 1797-1903) and Cole (Cancer Res., Dec. 1, 1997, Vol. 57, pg 5320-5327), all of record, who describe the variable and diverse nature of TIL TCRs.

Applicants argue no evidence has been provided to support the inherency argument put forth by the examiner. Therefore, applicants conclude the interpretation is in error. Applicants' argument is not persuasive. The patent office does not have the ability to test the TIL described by Nishimura for their reactivity with cells of other mouse strains. Shileyansky, Nishimura, Wang and Cole, all of record cited above, supports the diversity of TIL TCRs. While the TCR repertoire may be "restricted" or "limited" as described by some of the references known in the art, the TCR repertoire of TIL is still "variable" and may be represented by nearly every TCR variable region subset. Therefore, without evidence to the contrary, the TIL would be reactive with allogeneic cells as claimed and have an "endogenous TCR that is reactive to a cell that is allogeneic" to the TIL.

Interpretation 3: the transduced mouse TIL have two receptors: the MOv- γ chimeric receptor and an endogenous T-cell receptor that recognizes FBP (the antigen with which the TIL are stimulated). The mouse TIL were stimulated with FBP antigen prior to transduction with the MOv-γ construct (col. 36, line 44, "antigen-stimulated TIL"). Therefore, the TIL described by Nishimura inherently have an endogenous TCR that would react with an allogeneic cell transfected to express FBP because they were stimulated with FBP antigen.

It is noted that Nishimura stimulated the transduced cells with 38 Tumor, 24JK, 24JK-FBP, IGROV and 888 MEL (col. 39, Table 8). However, 24JK and 24JK-FBP are not allogeneic as claimed because the Declaration by Dr. Hwu states they are syngeneic and not allogeneic to the TIL. IGROV and 888 MEL are not allogeneic as claimed because they are human cells and because allogeneic agents are from the same species (pg 11, line 8-9). The MC38 adenocarcinoma cell line (or 38 Tumor cells in Table 8) is not "allogeneic" as claimed because Robbins (Cancer Res. 1991, Vol. 51, No. 14, pg 3657-62) taught the cell line forms tumors in syngeneic C57Bl/6 mice (see abstract). Nishimura did not teach stimulating the TIL with allogeneic cells as claimed; therefore, claim 41 has been withdrawn from the rejection. However, stimulation with "allogeneic cells" is not required to meet the limitations in the product claims (1, 3, 4, 7, 8, 10, 11, 40 and 44-61 and 71). The TIL of Nishimura inherently have an endogenous receptor that would react with allogeneic cells expressing FBP.

Nishimura also taught human TIL (col. 38, lines 55-65), which is equivalent to claims 45, 47, 52, 61, 76.

Applicants argue TIL were not exposed to an allogeneic cell. Therefore, applicants conclude '755 does not teach every limitation of the claim. Applicants' argument is persuasive in regards to claim 41 which expressly requires contacting the lymphocytes with an allogeneic cell. However, applicants' argument is not persuasive in regards to the product claims, which do not require contacting the lymphocytes with an allogeneic cell. The TIL of Nishimura stimulated with FBP is equivalent to the lymphocyte claimed because the TIL of Nishimura would recognize allogeneic cells expressing FBP.

III. Claims 1, 3, 7, 8, 11, 40, 41, 45-47, 50, 52, 56, 58, 61 and 71 remain rejected and claims 72 and 75-82 are rejected under 35 U.S.C. 102(e) as being anticipated by Capon (US Patent 6,407,221, June 18, 2002, filed 6-7-95).

Capon taught a primary human CD8+ lymphocyte transduced with a vector encoding a chimeric receptor that recognizes a tumor antigen (col. 5, lines 26-29; col. 11, lines 41-44; col. 11, line 66, through col. 12, line 8; col 12, line 40; col. 31, line 37-44; claim 2). The cells were stimulated with the human kidney cell line 293 (col. 31, lines 60-67). Capon used the HIV protein gp120 as an antigen in tumor cells; therefore, the gp120 protein is a "tumor antigen" in the teachings of Capon.

The lymphocytes taught by Capon inherently have a second receptor that is an endogenous T-cell receptor reactive with the allogeneic cell line 293 used to stimulate the lymphocytes. The second receptor would recognize human PBMC, dendritic cells and splenocytes (claims 8, 46, 50, 56, 58) having the same MHC molecules as the

allogeneic cell line 293 used to stimulate the lymphocytes. Therefore, the lymphocytes have an endogenous receptor that reactive with allogeneic PBMCs, dendritic cells or splenocytes as claimed.

Applicants argue the term "tumor antigen" is limited to a molecule that can be used to target therapy against a tumor in vivo. Applicants point to the discussion of "tumor antigens" on pg 13 which states:

> "A tumor antigen can be defined as a molecule that can be used to target therapy against a tumor and includes those antigens only found on tumor cells (i.e. tumor specific), those which are expressed on tumor cells and on limited normal tissues, i.e. differentiation antigens (including cancer-testis antigens) and those which are over-expressed on tumor cells compared to the expression on a wide variety of normal tissues (i.e. over- expressed antigens). Examples of over-expressed antigens include, but are not limited to, Folate binding protein (FBP), Erb-B2, GD-2, HMW-MAA, G250, TAG-72, NY-ESO-I, carcino-embryonic antigen and alpha-fetoprotein." (pg 13).

Applicants conclude the gp120 protein is not a tumor antigen because it is not expressed in a tumor cell and thus, Capon does not teach all the limitations of the claimed invention. Applicants' argument is not persuasive. The CD8 recognize gp120 expressed on tumor cells (col. 32, lines 50-59). Therefore, gp120 is a "tumor antigen" as discussed on pg 13 of the specification because it is molecule used to target tumor cells.

Applicants argue the assertion of inherency by the examiner (that the lymphocytes described by Capon have an endogenous TCR that would recognize an allogeneic cell) is not supported by evidence. Therefore, applicants assert that inherency has not been demonstrated. Applicants' argument is not persuasive. Capon stimulated the lymphocytes with the human kidney cell line 293. Without evidence to

the contrary, the 293 cell line is "allogeneic" to the lymphocytes because they were isolated from a different individual and have different MHC molecules. Applicants have provided no evidence to dispute the assertion of inherency made by the examiner. The patent office does not have the ability to test the cells for the endogenous receptors in the lymphocytes described by Capon. Therefore, the reasoning provided by the examiner is adequate to maintain the assertion of inherency.

IV. Claims 1, 3, 7, 8, 11, 40, 41, 45-47, 50, 52, 56, 58, 61 and 71 remain rejected and claims 72 and 75-82 are rejected under 35 U.S.C. 102(e) as being anticipated by Capon (US Patent 5,359,046, Oct. 25, 1994, filed 12-9-92) for reasons of record.

Capon taught a primary human CD8+ lymphocyte transduced with a vector encoding a chimeric receptor that recognizes a tumor antigen (col. 11, lines 48-56; col. col. 12, line 7-16; col 12, line 45-52; claim 6). Capon used the HIV protein gp120 as an antigen in tumor cells; therefore, the gp120 protein is a "tumor antigen" in the teachings of Capon.

The transformed population of cells taught by Capon inherently has a second receptor that is an endogenous T-cell receptor reactive with a cell that is allogeneic to the lymphocyte. The lymphocytes taught by Capon inherently have a wide array of T-cell receptors and, therefore, must inherently have endogenous receptors that recognize cells from a human having a different MHC genetic background. Non-transduced primary human CD8+ lymphocytes would recognize any human cell that had a different MHC molecule, including PBMC, dendritic cells and splenocytes

(claims 8, 46, 50, 56, 58, 75). Therefore, the gene-modified primary human CD8+ lymphocytes would also recognize any human cell that had a different MHC molecule.

Applicants argue there is no evidence that the T-cells have an endogenous TCR reactive with an allogeneic cell. Applicants' argument is not persuasive. The examiner has provided adequate logic and scientific reasoning why the cells have the TCR in question. Since the Patent office does not have the ability to test the lymphocytes for their ability to react with allogeneic cells, without evidence to the contrary, the inherency asserted by the examiner is maintained.

Conclusion

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached at the office on Monday, Tuesday, Thursday and Friday from 9:30 am to 6:00 pm at 571-272-0738.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on 571-272-0735.

The official fax number for this Group is (571) 273-8300.

Michael C. Wilson

MICHAEL WILSON
PRIMARY EXAMINER